the genetic alteration of the potato to express the NEPA, in combination with an orally effective adjuvant, said combination causing an immune response to oral administration specific to the NEPA stronger than a response specific to NEPA caused by the NEPA alone.

Please cancel claims 2, 6, 11, and 12.

Please change the dependency of Claim 7 from "6" to --3--.

Remarks

This is in response to the official action of October 3, 2000.

The withdrawal of the rejection of claims under 35 U.S.C. 112, of the rejection of Claims 1, 3 and 5-12 under 35 U.S.C. 103, and of Claims 1-2 and 4-12 under 35 U.S.C. 103 is noted with appreciation.

Claims 1-3 and 5-12 have been rejected under 35 U.S.C. 112 first paragraph for lack of enablement. **This is a new ground of rejection not made necessary by any amendment of the Applicants and has therefore improperly been made final.** The amendment is based upon the allegation that enablement is not provided for providing an immune response to non-enteric pathogens selected from the group consisting of hepatitis C, hepatitis delta, yellow fever, dengue Homeric fever, tetanus, staphylococcus aureous, yaws, relapsing fever, rat bite fever, bubonic plague and spotted fever (listed in claim 3 only). Since the specific NEP's are not listed in Claim 1, to which the rejection applies, it is assumed that the Examiner is applying the rejection to the NEPA language in general. Since this language was in original Claim 1, the rejection can in no way be considered necessary as a result of any amendment made by the Applicants.

The addition of this group of examples of non-enteric pathogens to claim 3 narrows the original claim ; therefore, a rejection based upon non-enablement should have been made in the original rejection. The amendment of the prior claims by the Applicants did not make the present rejection necessary. If the rejection were proper, it clearly would have been even more proper against the original claims.

In any case the rejection should be withdrawn since there is in fact clear enabling support in the specification.

The Examiner has said on page 7 that "Arntzen teaches methods of making a transgenic plant expressing an immunogen derived from Hepatitis B surface antigen...." and on page 8 "Koprowski also teaches that when the plant containing the NEPA is delivered, it can be delivered with an adjuvant to facilitate or improve its immunological therapeutic activity." Kaprowski is concerned with viral pathogens in general (see e.g. column 7, lines 18-47) but does not specifically mention hepatitis B. The Examiner states that the teachings of Kaprowski with respect to pathogens in general in combination with Arntzen and Stites make the present results "no more than a combination of known drugs administered by very old an (sic) well known methods in the art..."

It is difficult to reconcile the above statements and allegations of the Examiner with a position that the present application does not provide enablement. Enablement must be considered in light of knowledge available to one skilled in the art, including the teachings of the references cited by the Examiner. This is especially true since a number of prior art documents, including cited Arntzen patent 5,914,123, have been incorporated by reference. Almost the entire

Arntzen patent teaches how numerous plants can be genetically transformed to encode foreign genes and specifically teaches incorporation of antigens for poliomyelitis, measles, mumps, rubella, smallpox, yellow fever, hepatitis B, influenza, rabies, adenoviruses, Japanese b encephalitis, varicella, parvovirus, feline leukemia, etc. Similar teachings are given in the other patents incorporated by reference. **There is therefore more than sufficient teaching for making a transgenic plant required for use in accordance with the present invention as broadly as claimed and it is also clearly taught that the antigens made by such plants can function as vaccines when separated from the plant material and injected.**

What is not suggested in the cited art is how to make such transgenic plants orally function as vaccines and that is clearly taught in the present application, i.e. use a potato and an effective oral adjuvant as clearly taught in the specification. ***The invention is thus clearly enabled.***

Claims 1 and 4-18 have been rejected under 35 U.S.C. 103 as being unpatentable over Arntzen et al. (B) in view of Koprowski et al. (A), and further in view of Stites et al. (U).

Arntzen et al. teaches a method for making a transgenic tobacco, tomato or potato that expresses HBsAg.

Notwithstanding the Examiner's assertion, **Arntzen et al. does not teach "methods of making a transgenic plant expressing an immunogen derived from hepatitis B surface antigen, wherein the immunogen is capable of eliciting an immune response in an animal by consumption of the plant material."**

Arntzen et al. pays lip service to raising an immune response by ingestion, but in fact give no examples or teachings for obtaining such a result. **The only actual plant examples in Arntzen et al. relate to tomatoes and tobacco. There is no example of ingestion of either one and certainly no example showing that ingestion of either raises an immune response.** In fact, ingestion of the transgenic tomato does not raise any significant immune response (see the enclosed Rule 132 Declaration of Dr. Yasmin Thanavala) and certainly tobacco cannot be used for such a purpose because it is toxic. **Since there is no teaching in Arntzen et al. of how oral immunization to HBsAg or anything else might be accomplished using a transgenic plant, and in fact the plants made in the examples do not function orally to raise an immune response, as Arntzen et al. alleges, it is clear that there is insufficient teaching or suggestion in Arntzen et al. to support a rejection of the present claims** whether the reference is considered alone or in combination with the other cited references.

Simply making an unsupported allegation in a reference without a teaching as to how the allegation might be accomplished, is not a sufficient teaching to make a method for accomplishing the desired result obvious to one skilled in the art. Prophetic statements cannot be used to form the basis of a rejection, especially when they are unsupported and not true.

Arntzen et al. itself teaches and recognize that not all antigens would cause an immune response if ingested.

Arntzen et al. says in column 15 beginning at line 27,

"The vaccines are conventionally administered parenterally, by injection, for example either subcutaneously or intramuscularly. Additional formulations which are suitable for other modes of administration include suppositories and, ***in some cases***, oral formulations or aerosols." (emphasis added).

But there is no teaching or suggestion in Arntzen et al. of how the "some cases" could be determined or how the "some cases" could be accomplished.

While Arntzen et al. suggest that tomato juice containing HBsAg might be used as a vaccine, in fact Arntzen provides no supporting data showing any immune response whatsoever to tomato juice or any other plant containing HBsAg. To the extent that Arntzen teaches that tomato juice or any other plant material containing HBsAg can be used as a vaccine, it is an inoperative reference since there is no teaching or suggestion as to how that might be done. ***Simply ingesting the plant material, as suggested by Arntzen et al., does not confer immunity*** at least in the sense that there is a protective response.

There is good reason for Arntzen's omission of data showing a protective immune response to HBsAg by ingesting food material containing it, since prior to the present invention, in fact, there was little if any immune response whatsoever to HBsAg in orally ingested tomato juice or any other plant expressing HBsAg. See the enclosed Rule 132 Declaration of Dr. Thanavala. The response, if any, is clearly insufficient for the purpose of the present invention.

Reference to the examples in the present specification clearly illustrates that priming of the subject of the immunization is required by either pre-vaccination or the use of an effective adjuvant. Arntzen et al. suggests neither. Arntzen et al. doesn't suggest an adjuvant for any purpose whatsoever and certainly does not suggest a combination with an adjuvant that permits the obtaining of a high immune response to orally administered HBsAg as required by the present claims.

Arntzen's suggestion of simple ingestion of plant material expressing HBsAg gives little if any immune response and certainly does not give a sufficient immune response to be considered protective. Arntzen discloses or suggests no way in which a high immune response could be orally obtained.

The Examiner states that Koprowski "teaches methods of making microbially transfected plants expressing a viral antigen which is fed to an animal or human to elicit an immune response." **Koprowski at al. does not teach or suggest any method for making a transgenic plant as required by the present claims** but teaches a microorganism expressing a bioactive compound, e.g. an immunogenic rabies polypeptide. The microorganism may then be used to infect a plant as a parasite but does not alter the genetic character or expression of the plant.

Kaprowski et al. suggest that their method has wide application, e.g. for treatment of viral infections, bacterial infections, fungal infections, protozoan infections, diabetes, immune disorders, cancer and heart disease. Kaprowski et al. more specifically suggest that their method could be used for mucosal pathogens, e.g. rabies, respiratory syncytial virus, cholera. typhoid fever, herpes simplex types I and II, tuberculosis, pathogenic pneumococci, human immunodeficiency virus-1 (HIV-1) and human immunodeficiency virus-2 (HIV-2).

The only specific example given is for rabies which is not considered a nonenteric pathogen in accordance with the present invention since it can invade enterically. There is no enablement for the other suggested applications. If the disclosure actually enabled everything suggested, oral vaccines effective against Aids, cancer, and herpes, among many others, would

be made available simply by following the teachings of the Kaprowski et al patent. It is well known that this is not the case.

Kaprowski et al. certainly does not enable or even reasonably suggest application for orally raising an immune response to an antigen by feeding a transgenic plant. The suggestion that an adjuvant be used is a gratuitous statement applied across the entire non-enabled spectrum of the Kaprowski et al. disclosure. There is no suggestion of any specific adjuvant that would have such an effect for purposes of enablement and in fact there is no suggestion that any adjuvant would have any effect whatsoever upon oral immune response to antigens of non-enteric pathogens of the present claims. Adjuvants that can be used in injected vaccines rarely have any significant effect when administered orally.

Stites et al. adds nothing to cure the inadequate teachings and suggestions of Arntzen et al. and Kaprowski et al. Stites et al. does not suggest anything concerning orally raising an immune response to an antigen expressed by a plant. Further, Stites et al. clearly does not suggest any method for **orally** raising a highly effective immune response in the presence of a suitable adjuvant as presently claimed. Adjuvants may "enhance" immune response but in the absence of an immune response to be enhanced, have no effect. Arntzen does not teach any method showing any oral immune response to be enhanced by an adjuvant.

In view of the foregoing amendments and remarks, it is courteously requested that all rejections be withdrawn and all claims be allowed.

Respectfully submitted,

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